IN THE UNITED STATES PATENT OFFICE

Application Serial No. 07/675,908

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Applicants: Dr. Rudolf Falk
Dr. Samuel S. Asculai
(Now assigned to Hyal Pharmaceutical Corporation)

Title: THE USE OF HYALURONIC ACID OR ITS DERIVATIVES TO ENHANCE DELIVERY OF ANTINEOPLASTIC AGENTS

Inventors: Dr. Rudolf Falk,
Dr. Samuel S. Asculai

Examiner: Dr. Jacqueline Krikorian Ph.D. (*formerly* Dr. Stephen Martin, Ph.D.)

Group Art Unit: 1806 Extended Due Date: September 5, 1996

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 Jefferson Davis Highway
Crystal Plaza 2, Room 1B03
Arlington, Virginia
U.S.A. 22202

DECLARATION OF EVA TURLEY
under § 1.132

I, EVA TURLEY, make oath and say as follows:

1. (a) I have a Ph.D. in cell biology and conduct and have conducted extensive research in the area. I am presently a Professor at the University of Toronto for the Department of Anatomy and Cell Biology/Pathology and Senior Scientist at the Hospital for Sick Children at Toronto, Ontario. I have written extensively with respect to hyaluronic acid. Now shown to me and marked as Exhibit 1 is a copy of my curriculum citae. As a result of my experience, I consider myself to be an expert in respect of Hyaluronan.

2. Prior to about 1989, I was aware that Hyaluronan (Hyaluronic Acid) had been used for intra articular injections at very high molecular weights (over 2,000,000) for administration to the intra articular cavity to prevent cartilage degradation of the joint. I was also aware that in the latter part of the 1980's, it was known that Hyaluronic Acid, when applied topically for example to the eye, permitted a slow release of a substance carried by the Hyaluronic Acid for absorption by the eye proximate the application of the formulation. My understanding was that the Hyaluronic Acid would be retained on the cornea non-specifically where it was applied to the cornea, and permit the substance carried by the eye to leak therefrom and be absorbed by the local area to which it contacts. This type of approach is disclosed in United States Patent No. 4,736,024, a copy of which I was asked to examine, and I will have more to say about this approach later in my Declaration. In any event, by the late 1980's, Hyaluronic Acid had been proposed to be used as a vehicle for substances which were to provide a retard effect to the release of the substance due to the viscosity of this polymer at clinical concentrations. The substance was then absorbed for use. There was no indication of an active contribution by Hyaluronic Acid to the transport or delivery of the substance other than by being an excipient for the substance applied at the site and from which the substance leaked. The substance was absorbed when it difused from the Hyaluronic Acid. The substance was not transported, delivered, or actively released by the Hyaluronic Acid to any sites in need of treatment.

3. In or about 1990/1991, I became aware of an invention of Drs. Falk and Asculai which had determined that dosages comprising Hyaluronic Acid having at least minimum amounts of forms of Hyaluronic Acid having specified molecular weights did in fact transport and deliver medicines and therapeutic agents to sites of diseases and conditions in need of treatment, and for example

with respect to the treatment of cancer were obtaining positive results in patients that were terminally ill. This finding totally surprised me. This finding was unexpected with regard to the previous state of the art with respect to Hyaluronic Acid. I have since that time learned that the Falk and Asculai development has been incorporated in a patent application, International Application No. PCT/CA90/00306, published under International Publication No. WO 91/04058 and which has entered the national phase, I am advised by Ivor Hughes, counsel to Hyal Pharmaceutical Corporation, in the United States Patent Office under Application No. 07/675,908. I have been advised by the said Ivor Hughes that the said United States Application 07/675,908 has been assigned to Hyal Pharmaceutical Corporation. I have been given a copy of International Publication No. WO 91/04058 and have been asked to give my comments with respect to the teachings thereof.

4. This document confirms my understanding of the development I learned of in the early 1990s referred to in paragraph 3. Subsequent to that date, I have been retained by Hyal Pharmaceutical Corporation to act as a consultant and conduct experimentation, and have been identified as an inventor of subject matter of inventions incorporated into applications filed on behalf of Hyal Pharmaceutical Corporation. I have assigned my interest in those applications to Hyal Pharmaceutical Corporation. I am also a Director of Hyal Pharmaceutical Corporation whilst retaining my appointment at the Hospital for Sick Children in Toronto as an independent scientist. I value my international reputation and, therefore, being a Consultant and Director does not change my obligations as a professional when providing this declaration and does not interfere or cloud my professional objectivity and responsibilities in preparing this declaration or preparing my opinion.

5. I have examined International Publication No. WO 91/04058 and have determined that the invention in my opinion disclosed therein relates to dosages containing Hyaluronic Acid or salts thereof together with the medicine in effective amounts. The Hyaluronic Acid and salts thereof are present in varying doses from 10 mg/70 kg person to 1000 mg/70 kg person with optimal doses tending to range between 50 and 350 mg per 70 kg individual discussed at page 26, line 32 to 35. The molecular weights of the form of Hyaluronic Acid used in the dosages are from 150,000 daltons to less than 750,000 daltons. One amount of Hyaluronic Acid is a 2% solution with a mean average molecular weight of about 225,000 referreed to at page 29 of the application. The dosages of the medicine or therapeutic agent may be known amounts as would be understood by persons skilled in the art or a dose excess where in excess of 200 mg of the form of Hyaluronic Acid is present in the dosage form. See page 25, lines 20 and line 34 where the in excess amount of 200 mg of Hyaluronic Acid per 70 kg person is used in the dosage form. In the dosage administered to the patient, the side effects of, for example an NSAID, are decreased (see page 25, line 22), such as gastro-intestinal distress, neurological abnormalities, depression, etc. By administration of the dosages to patients in need of treatment for the conditions or diseases suffered by the patient, the Hyaluronic Acid alters the medicine's distribution and performance in the human body and produces an unusual targeting for underperfused tissue and pathological tissue, (page 24, lines 15 to 17).

6. In my opinion, persons skilled in the art reading the application would understand that Drs. Falk and Asculai have not developed a new medicine, but rather taken advantage of heretofore unknown enhanced ability of known medicines and therapeutic agents (and medicines and agents which will become known in the future for use with a specific disease) to reach the sites in need of treatment because in fact the Hyaluronic Acid targets the site in need of

treatment and delivers the medicine/therapeutic agent to the sites of the disease and condition.

7. Since the development of the invention, we have learned more about the mechanism of operation and action of the dosages and discovered that the liver and the sites of the disease or condition possess substantial unfilled receptors for Hyaluronic Acid, whereas normal tissue and cells contain very few unfilled receptors for Hyaluronic Acid. As a result, Hyaluronic Acid given to the patient targets the underperfused tissue and pathological tissue taking the medicine with it. This ability to deliver and transport the medicine is not disclosed in the prior art. Nor is there any recognition of same in the prior art.

8. I have written extensively in regards to the receptors, and one of my publications relates to the receptor RHAMM for which I filed a Patent Application and for which I have been identified as an inventor.

9. In my opinion, persons skilled in the art would have no trouble preparing the dosage amounts taught in International Publication No. WO 91/04058and administering the dosage amounts taught by the application to the patients.

10. Hyaluronic Acid occurs naturally as a salt, and particularly it is hard to obtain Hyaluronic Acid as a non-salt. The expression Hyaluronic Acid itself already includes Hyaluronic Acid in salt form as would be understood by persons skilled in the art. The use of the expressions "pharmaceutically acceptable salts of Hyaluronic Acid", "non-toxic salts of Hyaluronic Acid" and "salts of Hyaluronic Acid" would in my opinion be interchangeable having regard to the teachings of International Publication No. WO 91/04058 and practices in the profession with respect to the treatment of patients. Persons treating patients would only use

non-toxic salts and non-toxic amounts of the salts to treat the patients. This is implicit in the teachings in the application.

11. In the treatment of cancer, the cases referred to beginning at page 36 clearly indicate that the patient had been unresponsive to conventional treatment. To me that means that the persons were terminally ill, and that unless the new treatment was successful, the patients would die as a result of the disease. These patients were subsequently treated with the formulations of the invention of International Publication No. WO 91/04058. The patients' conditions improved. Some went into remission.

12. With respect to the molecular weights of the Hyaluronic Acid used and taught in the application, it is clear that while there may be differences with respect to the extremes of molecular weights of Hyaluronic Acid, those referred to in the application between 150,000 daltons and 750,000 daltons would generally perform in the same way, and persons skilled in the art would do some minor (minimal) adjustments when choosing the form of Hyaluronic Acid and its molecular weight to achieve the desired dosages. Persons skilled in the art further would not have a concern about the dosages employing the Hyaluronic Acid, because the molecular weights and concentrations of the Hyaluronic Acid used as taught in the application are not very viscous in the first place, and such persons would dilute the Hyaluronic Acid because of the addition of the medicine and the excipients necessary to bring the medicine into the dosage form. As a result, in my opinion, persons skilled in the art would have no difficulties in preparing the dosages taught in the application so that they were easily administered to the patients irrespective of whether the dosages were to be systemically administered or topically administered. If any adjustment would be required, such adjustments would be minimal and within the competence of the practitioner.

13. I have also examined a copy of an article I understand was referred to by the United States Examiner, West et al., 1989. I was familiar with this article before the presentation to me by Ivor Hughes counsel for Hyal Pharmaceutical Corporation, and in my expert opinion, the article is controversial. Toole, et al. found that they cannot duplicate the results. Moreover, in a conversation with a scientist at a recent Gordon Conference, the Hyaluronic Acid polymer is dominant in its biological effects. In any event, the lower molecular weights of Hyaluronan used in the dosages is in the order of about 150,000 daltons, not an amount of concern by West et al.

14. Hyaluronic Acid, as well, is not very toxic. In very rare cases, the Hyaluronic Acid can cause mesophyliomas where the molecular weight of the Hyaluronic Acid is very high. However, because the blood breaks down the large molecular weight molecules of the Hyaluronic Acid and because such conditions are very rare, the amount of Hyaluronic Acid is unlikely at the levels indicated in the application to cause any problems.

15. I have also been asked to comment with respect to spontaneous remission. When dealing with the treatment of patients such as those terminally ill with cancer or AIDS, it is totally appropriate to use historic controls, namely those that if the patient is terminally ill, it is assumed that the patient will die. Hence, the statement at page 36, lines 4 to 6, dealing with the cancer cases, it was expected that the patients would die. Spontaneous remission is a very rare occurrence, and, therefore, has no meaning when dealing with the cancer case studies that were given as examples in the application.

16. Therefore, it is clear to me that persons skilled in the art would be able, reading International Publication No. WO 91/04058, to duplicate them with

respect to the treatments of diseases and conditions. Persons skilled in the art would have no difficulty in doing so. This is because the invention targets the disease or condition site in need of treatment transporting or delivering the medicine to the underperfused tissue and pathological tissue. By providing this targeting of the medicines to the site in need of treatment, I believe that the targeting effect enables a reduction in side effects of medicines, for example NSAIDS. Thus, the at least 200 mg of Hyaluronic Acid targets the site with, for example the NSAID, which may have side effects (not the desired effect) of the medicine such as gastro intestinal distress, neurological effects, etc. which do not materialize because of the targeting effect. While an example is given at page 53 (Case XIX) where the patient suffered heartburn, taking in excess of 300 mg of indomethacine dissolved in 300 mg of Hyaluronic Acid and the amount was reduced to 100 mg, both the 300 mg and 100 mg are excess dosage amounts of the indomethacine NSAID and the effects on patients will be different. In case XIX, there appears to have been a heartburn in the patient which was caused by the excess dosage amount of 300 mg which was reduced to the excess dosage amount of 100 mg. In case XVIII, 300 mg of indomethacine was given to the patient in 300 mg of Hyaluronic Acid, and there appears to have been no problems with the patient taking 300 mg of indomethacine in 300 mg of Hyaluronic Acid. It is therefore clear that the side effects are reduced, that the patient who suffered heart burn taking 300 mg of indomethacine suffered from side effects which may have still been considerably less and probably were considerably less than those that would be normally suffered by the taking of the excess dosage amount of 300 mg of indomethacine. It is also clear from the teachings of the International Publication No. WO 91/04058 that persons using the drug for the treatment of a disease which has now been targeted by putting it into a dosage form with Hyaluronic Acid, know what side effects are exhibited by the drug and what effects are being reduced. In my opinion, persons skilled in the art would have no difficulties formulating the dosages as taught by International Publication No.

WO 91/04058 or administering the dosages in a treatment for treating the disease or condition for which the drug is being given as treatment.

17. I have also been asked to review four references, namely Della Valle, et al., United States Patent No. 4,736,024; Seifter, U.K. Patent No. 769287; Schultz, United States Patent No. 4,808,576; and Balazs, Hyaluronic Acid, Its Structure and Use, Polymers in Chemistry, 1984, Volume 99, pages 65 to 72.

18. Della Valle, United States Patent No. 4,736,024 teaches the use of Hyaluronic Acid in dosages including a medicine which does not when administered target the site of a disease or condition. These dosages when applied to the cornea simply adsorb non-specifically to the surface only where applied and do not target. The medicine is permitted to leech (leak) therefrom, and the Hyaluronan present provides an excipient effect. Persons skilled in the art would so understand the teachings of Della Valle, United States Patent No. 4,736,024, and would not think otherwise. Della Valle provides a gel which emulsifies the medicine and subsequently releases the medicine for absorption on the eye. This is clear from the teachings at column 1, lines 46 to 53, and column 2, lines 44 to 51 of the said reference. The only examples given are those relating to the topical treatment of the cornea of the eye. In this regard, small amounts of less than 1 mg of Hyaluronic Acid is to be found in each dosage amount. This is clear from reading column 27, line 57 (micro syringe (10 mcl)); column 29, line 30 (micro syringe (10 µl)), column 30, line 37 (1 drop (50 µl)), which are microlitres; column 31, line 52 (3 drops), and column 33, line 23 (2 drops). One statement is very appropriate, that found at column 30, line 65 "Transcorneal penetration of Pilocarpine seems therefore to depend on the capacity of Hyaluronic Acid to vehicle a drug forming a homogeneous and stable film on the cornea." It is implicit to me that the Hyaluronic Acid assists to provide a film from which the medicine carried in the film of Hyaluronic Acid

leeches (leaks) and which Pilocarpine medicine is then absorbed non-specifically by the eye (i.e. is not specific). The teachings of Della Valle are directly opposed to the teachings of International Publication No. WO 91/04058.

19. United States Patent No. 4,808,576 (Schultz) teaches the use of Hyaluronic Acid as a therapeutic agent only. It is administered for the purposes of treating conditions which were known to be treatable by the use of Hyaluronic Acid only that the administration takes place at a site remote from the site in need of treatment. However, this remote administration of Hyaluronic Acid topically is not and cannot be effective without the use of a transdermal carrier, see column 6, line 3, and column 12, lines 14-17. Schultz specifically states that the topical application of the sodium hyaluronate without a transdermal carrier was ineffective, column 12, lines 14 and 15. The transdermal carrier preferred is DMSO and is used in the examples. DMSO is the unique molecule which when applied topically carries material with it which is to be delivered systemically. DMSO is also an analgesic (sodium silicate as well one of the transdermal carriers is also an analgesic). Thus the DMSO delivery of Hyaluronic Acid as the therapeutic agent, wherein the DMSO is analgesic makes all results of topical application more than suspect.

20. Additionally, with respect to systemic administration, only two examples are provided. Example 1 provides the use of Hyaluronic Acid having a molecular weight of 1.88×10^6 daltons. There appears to be some success. However, Comparative Example 1, beginning at column 13, casts doubt on the effects provided.

21. In any event, Schultz teaches the use of Hyaluronic Acid wherein the Hyaluronic Acid is the therapeutic agent and nothing more.

22. Neither Della Valle nor Schultz teach the targeting of anything by the use of Hyaluronic Acid.

23. It is not clear in either Schultz or Della Valle that they can target drugs systemically. They have done nothing to assess this in that regard.

24. Seifter, U.K. Patent No. 769287 clearly provides that partially depolymerized Hyaluronic Acid (PDHA) works to spread the agent carried thereby (and thus dilutes the agent and spreads it over a larger area), but that Hyaluronic Acid which has not been partially depolymerized does not work. Having regard to the teachings of Seifter, it is my opinion that PDHA would have no affect on the receptors of a disease site or a site suffering a condition and therefore could not be used to transport medicine and target the medicine to the site of the disease focus or condition focus.

25. The Balazs article entitled "Hyaluronic Acid: It's Use and Structure" adds nothing.

26. In view thereof, it is my opinion that even if the teachings of the various references are combined (which I do not see possible), the references do not in any way allude to, suggest or in any way teach the targeting of medicines and therapeutic agents by their administration with Hyaluronic Acid to a site in need of treatment.

27. This targeting by Drs. Falk and Asculai in International Publication No. WO 91/04058 is achieved using dosages containing between about 10 mg and 1000 mg (or more) of Hyaluronic Acid or a salt having a molecular weight between 150,000 daltons and about 750,000 daltons and containing an effective amount of a medicine/therapeutic agent.

28. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements will jeopardize the validity of the application and any patent issuing thereon.

EXECUTED this 21 day of August, 1996.

EVA TURLEY

EXHIBIT 1

CURRICULUM VITAE

NAME: Eva A. Turley, HBSc., Ph.D. (Cell Biology)

DATE OF BIRTH: March 7, 1950

EDUCATION:

1972	University of British Columbia, HBSc.
1976	University of British Columbia, Ph.D. (Cell Biology)

PROFESSIONAL EXPERIENCE:

1996 - Present	Senior Scientist, Sick Children's Hospital Professor, University of Toronto, Department of Anatomy and Cell Biology/Pathology
1993 - 1996	Professor, Department of Pediatrics, University of Manitoba
1990 - 1996	Senior Scientist, Manitoba Institute of Cell Biology
1990 - 1993	Tenured Associate Professor of Pediatrics, Professor of Physiology, University of Manitoba
1986 - 1990	Associate Professor, Department of Pharmacology, University of Calgary; Senior Scientist of the National Cancer Institute of Canada.
1986 - 1987	Sabbatical Leave, Department of Biochemistry, University of Alabama at Birmingham
1980 - 1986	Research Scholar of the National Cancer Institute of Canada
1980 - 1986	Assistant Professor, Department of Pharmacology, University of Calgary
1979 - 1980	Postdoctoral Fellow in the Department of Biology, University of Oregon

1976 - 1979	National Cancer Institute of Canada Postdoctoral Fellow (King George V Silver Jubilee Citation). Department of Biology, Johns Hopkins University

AWARDS:

1991 - present	Children's Health Research Foundation Scholar
1988	YWCA Woman of Distinction Award, Calgary
1986 - 1990	Senior Scientist, National Cancer Institute of Canada
1986	Heritage Scientist (declined)
1980 - 1986	Research Scholar, National Cancer Institute of Canada
1976 - 1980	National Institute of Canada Postdoctoral Fellow
1976	N.C.I. King George V Silver Jubilee Citation for top applicant in Canada
1974 - 1976	H.R. McMillan Graduate Student Fellowship

PROFESSIONAL SOCIETIES:

American Society for Cell Biology

American Society for Complex Carbohydrates

PROFESSIONAL ACTIVITIES:

Current:

1996 -	NRC Council
	US Army Breast Cancer Panel
	Heart and Stroke Foundation Grants Panel
	NCIC Grants Panel B

	Numerous Site Visits
1992 - Present	Board Member, Advisory Research Group, Hyal Pharmaceuticals
	Evaluation Committee for Directorship of A.H. Greenberg
	Reviewer, Health Sciences Centre Foundation
	Committee for Breast Cancer
	Panelist MRC Pathology and Morphology (1993 -)
	Panelist NCIC Cell Biology and Metastasis (1990 - 1994)
	Committee member for 4 Ph.D. students (Drs. Kardami, Wilkins, Litchfield and Nagy, supervisors)
	B.Sc. (Med.) Prize Committee
	Children's Health Research Foundation Grants Panel
	Tenure Committee, Dept Physiology
	Graduate Student Committee, Physiology
	CHRF, Board of Directors
1991 - Present	Health Sciences Center - Child Health Executive Committee
	Alberta Cancer Board, BC Health Research
	MRC External Review, NIH External Review and Site Review
1990 - 1994	MHRC Grants Panelist
1990 - Present	Medical Advisory Committee, Children's Hospital Research Foundation
	Cancer Cell Biology Course, Lecturer
1985 - Present	Reviewer/Guest Editor for:
	Developmental Biology Biochem. Biophys. Acta.

J. Cell Biol.
In Vitro
Cancer Metastasis Reviews
Exp. Cell. Res.
J.N.C.I.
Int. J. Cancer
J. Biol. Chemistry
Oncogene
MCB
Development
J. Clinical Investigation
American J. Pathology
Hematology
Am. J. Respiratory Cell and Molecular Biology

Past Service:

1992 - 1995	MRC Grants Panel Morph. Pathol.
1991	NIH Grants Panelist RO3 Cancer, Molecular and Cell Biology
	Dean's Search Committee for Biochemistry Chair
1990	Judge of Pediatrics Residents and Fellows Research Symposium
	External Reviewer, NIH Site Visit, University of California, San Francisco Breast Cancer Group
	External Reviewer, NIH Site Visit, Harvard
	External Reviewer, Ph.D., University of Alberta
1989 - 1990	Chair, Undergraduate Medical Research Program, Corporate Committee, Alberta Cancer Board
1988 - 1990	Research Committee, Alberta Cancer Board
	Space Committee, University of Calgary Medical School
1987 - 1990	Head, Metastasis Research Group; Ethics Committee, University of Calgary
	Corporate Committee, Alberta Cancer Board

1987 - 1990	Head, Metastasis Research Group; Ethics Committee. University of Calgary
1980 - 1990	Lecturer, Medical Undergraduate Systems Course: Teratology, Connective Tissue and Adrenal Gland Sections
	Lecturer, Undergraduate Research Seminar Course, Department of Biology
	Lecturer, Pharmacology Graduate Course
1980 - 1985	Lecturer, Developmental Biology
1980 - 1985	Grants Panel, Alberta Cancer Board
1980 - 1984	NCIC, Grants Panel B

INVITED LECTURES AT MEETINGS (1980 - PRESENT):

1980	Department of Anatomy, Harvard, Boston
1980	Department of Pathology, Queen's University, Kingston, Ontario
1981	Department of Anatomy, UBC, Vancouver
1982	Hotel Dieu, Quebec City, Quebec
1983	Department of Biology, University of California at Davis
1984	International Conference for Developmental Biology, Southhampten, UK
1985	Diabetes Hospital, University of Alabama, Birmingham, Alabama, USA
1986	1st Conference on Hyaluronan, St. Tropez, France
1987	Department of Anatomy, UBC, Vancouver
	Manitoba Institute of Ce' Biology, Winnipeg

Mt. Sinai Hospital, Toronto

McKechern Cancer Group, University of Alberta

Department of Biochemistry, University of Arizona, Tuscon

1988 Ciba Foundation, London. England

Society for Complex Carbohydrates, Ann Arbor

3rd Proteoglycan Gordon Conference, Andover

1989 Department of Pathology, University of Washington, Seattle

Southern Connective Tissue Meeting, Tampa

1990 International Conference on Cell Differentiation. Vancouver

4th Proteoglycan Gordon Conference, Andover

Manitoba Institute of Cell Biology, Winnipeg

Department of Biology, University of Minnesota, Minneapolis

Hospital for Sick Children, Toronto

Institute for Muscular-Skeletal Development, Washington, DC

Heritage Day, Joint Injury and Disease Lecture, University of Calgary, Calgary

Department of Biology, University of Calgary

American Cell Biology Meetings, San Diego

Department of Immunology, University of Alberta

1991 Lecturer at Graduate Course in "Biolc ,y of Hyaluronan", Satra Brun, Sweden (Upsala

Universitet)

Department of Anatomy, University of Kuopio.
Kuopio, Finland

Department of Biochemistry, University of Manitoba

Manitoba Institute of Cell Biology, Manitoba Cancer Foundation

Human Genetics, University of Manitoba

Mini Sympposium on Extracellular Matrix, University of Manitoba

Department of Pediatrics Seminar Series

1992 Division Cancer Biology, Suny Brook Centre, Toronto

Hyal Inc., Toronto, 890 Yonge Street, Toronto

Department of Haematology, Vancouver General Hospital
Vancouver, Terry Fox Institute, Vancouver

Metastasis Talk, Department of Physiology Mini-Symposium
Radiation Oncology Research Seminar

Department of Immunology, UBC

1993 Upsalla, Pharmacia

Connective Tissue Meeting, Sweden

Hyal meeting, London, UK

Sick Children's Hospital, Toronto

University of N. Carolina, Chapel Hill

1994 Sick Children's Hospital, Toronto

Mayo Clinic, Phoenix

Department of Pathology, U of Washington

2nd International Meeting on Hyaluronan, Toronto

University of Tokyo. Japan

International Cartilage Meeting, Hiroshima, Japan

University of Nygoya, Nygoya

St. Bartholemew's Hospital, London, UK,
Department of Pathology, University of Washington, Seattle

1995 Western Pharmacology Society, Plenary Speaker, Hawaii

FASEB Meetings, Atlanta, Plenary Speaker, Hawaii

INWIN Meeting, Geneva

Hyal Round Table Meeting, Nyon

Keystone Meetings, Metastasis, Durango, Colorado

Medisone Co., Uppsala, Sweden

Pharmacia, Uppsala, Sweden

Biomedica Centrum, University of Uppsala, Sweden

Canadian Federation of Biological Sciences Meeting, Saskatoon

Gordon Conferences, Elastin Meeting, New Hampshire

Vascular Group, Sick Children's Hospital

Institute of Gerontology, Tokyo

University of Tokyo, Tokyo

Cell Adhesion Conference, Nagasaki, Japan

Dermatology Conference, Montreal

Rheumatoid Arthritis Conference, Israel

London Regional Cancer Centre, London, Ontario

1996 Keystone Meetings, Small GTP Binding Proteins, Durango, CO

American Association for Cancer Research. Cell Adhesion. Washington, DC

Swedish Connective Tissue Meeting, Medevi, Sweden

Canadian Society of Immunology, Sainte-Adele, PQ

Gordon Proteoglycan Conference, Andover, NH

Wenner-Gren Foundation, Stockholm, Sweden

PUBLICATIONS:

1. Slavinski, E.A., N. Auersperg and J.W. Jull. 1974. Propagation in vitro of functional rat adrenal cortical cells: modulation of the differentiated state with culture conditions. In Vitro 9:260-269.

2. Slavinski, E.A., J.W. Jull and N. Auersperg. 1976. Steroid pathways and trophic response to ACTH of cultured adrenal cortical cells in different stages of differentiation. J. Endocrinol. 69:385-394.

3. Slavinski-Turley, E.A. and N. Auersperg. 1978. Cultured adrenal cortical cells in various states of differentiation: electron microscopic characterization and ultrastructural response to ACTH. J. Endocrinol. 78:427-434.

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5. Turley, E.A. and S. Loth. 1980. Interactions between the carbohydrate chains of hyaluronate and chondroitin sulphate. Nature 283:268-271.

6. Pierce, M.J., E.A. Turley and S. Roth. 1980. Cell surface glycosyltransferase activities. Int. Rev. Cytol. 65:1-47.

7. Turley, E.A. 1980. The control of adrenal cortical cytodifferentiation by extracellular matrix. Differentiation 17:93-103.

8. Turley, E.A. 1981. A role of glycosaminoglycans in cell adhesion and movement. In Biology & Chemistry of Heparin (Lundblad, ed). Plenum Press. NY. 121-131.

9. Turley, E.A. 1982. Purification of a hyaluronate-binding protein faction that modifies cell socal behavior. Biochem. Biophys. Res. Commun. 108:(3) 1016-1024.

10. Erickson, C.A. and E.A. Turley. 1983. Substrata formed by extracellular matrix combinations alter neural crest motility in vitro. J. Cell Sci. 61:299-323.

11. Turley, E.A. and D. Moore. 1984. Hyaluronate binding proteins also bind to fibronectin, laminin and collagen. Biochem. Biophys. Res. Commun. 121:808-814.

12. Turley, E.A. 1984. Proteoglycans and cell adhesion: their putative role during tumorigenesis. Cancer Met. Review 3:325-339.

13. Turley, E.A. and M. Tretiak. 1985. Glycosaminoglycan production by murine melanoma variants in vivo and in vitro. Cancer Research 45:5098-5105.

14. Turley, E.A., C.A. Erickson and R.P. Tucker. 1985. Effect of matrix molecules on the structure of artificially prepared extracellular matrix. Dev. Biol. 109:347-369.

15. Turley, E.A., M.D. Hollenberg and R.M. Pratt. 1985. Effect of epidermal growth factor/urogastrone on glycosaminoglycan synthesis and accumulation in vitro in the developing mouse palate. Differentiation 28:279-285.

16. Turley, E.A. and J. Torrance. 1985. Localization of Hyaluronate and Hyaluronate-binding protein on motile and non-motile fibroblasts. Exp. Cell Res. 161:17-28.

17. Turley, E.A., P. Bowman and M. Kytryk. 1985. The effect of hyaluronate and a hyaluronate binding protein on cell motile and contact behavior. J. Cell Sci. 78:133-145.

18. Turley, E.A., D. Moore and L.J. Hayden. 1987. Characterization of Hyaluronate binding proteins isolated from 3T3 and murine sarcoma virus transformed 3T3 cells. Biochem. 26:2997-3005.

19. Turley, E., M. Tretiak and K. Tanguay. 1987. Effect of glycosaminoglycans and enzymes on the integrity of human placental amnion as a barrier to cell invasion. Journal of National Cancer Institute 78:787-795.

20. Erickson, C.A. and E.A. Turley. 1987. The effect of epidermal growth factor on neural crest monolayers. Exp. Cell Res. 169:267-279.

21. Turley, E.A. 1989. Hyaluronic acid stimulates protein kinase activity in intact cells and in an isolated protein complex. J. Biol. Chem. 264:8951-8955.

22. Turley, E.A. 1989. The role of a cell associated hyaluronan-binding protein in fibroblast behavior. The CIBA Fdn. Symposium No. 143. pp 121-134.

23. Turley, E.A., Roth, S. and Weston, J.W. 1989. Interactions among matrix molecules: possible mechanisms for structuring the extracellular matrix. Conn. Tis. Res. 23:221-235.

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PATENTS:

a)	PCT-/CA93/00158:	Use of RHAMM sequences and peptide motifs for diagnosis and therapeutics
b)	PCT (submitted):	Sequence of human RHAMM
c)	PCT (submitted):	Use of hyaluronan acid and forms to present arterial stenosis
d)	PCT (submitted):	Sequence of novel RHAMM isoforms that are transforming
e)	PCT (submitted):	Hyaluronic acid and forms to prevent tissue damage following inflammation
f)	PCT (submitted):	Use of hyaluronan mimetics to prevent excessive tissue damage
g)	PCT (submitted):	Use of oral hyaluronan to reduce neointima formation

Abstracts (not listed)

GRADUATE STUDENTS

		Degree	Position
1.	T. Allen	M.Sc. (1986 - 1988)	Medical Student
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6.	J. Entwistle	1992 -	Postdoctoral Fellow
7.	L. Klewes	1993 -	Postdoctoral Fellow
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